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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,220	07/14/2003	Nicholas M. Dean	ISPH-0751	7005

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,220	DEAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 78-84 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In the instant case, the effective filing date is determined to be that of the parent application of 09/802,669, which has an effective filing date of 03/09/2001. The instant case 10/619,220 does not receive the benefit of the earlier filing date of the following Patents: 6,653,133 and 6,204,055 because claims 78-84 of the instant case are not supported by the specification and claims of the previously mentioned parent applications. The parent applications, having Patent Nos: 6,653,133 and 6,204,055, disclose antisense compounds targeted to a nucleic acid molecule encoding Fas, methods of modulating Fas mediated signaling in cells and tissues using antisense compounds, methods of inhibiting Fas, FasL and Fap-1 and methods for diagnosing and treating autoimmune and inflammatory diseases, particularly hepatitis and cancer. Although the parent applications disclose SEQ ID NO. 73 as an antisense compound

targeted to mouse Fas, the disclosures of the parent applications failed to discuss prevention of ischemia reperfusion injury in a cardiac, renal, hepatic or skin allograft due to administering an antisense compound (SEQ ID NO. 73) targeted to a nucleic acid sequence encoding mouse Fas. Thus, the instant application 10/619,220 has an effective filing date of 03/09/2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 78 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 78 broadly reads on an antisense compound targeted to any nucleic acid sequence encoding any version of Fas from any organism. There is no specific description provided of an antisense sequence to any version of Fas which will bind to Fas, inhibit the expression of Fas, decrease apoptosis of the kidney cells of a mouse and treat or prevent a reperfusion injury of a mouse kidney caused by ischemia.

The specification as filed only teaches one mouse antisense compound (SEQ ID NO. 73) which at best only teaches a decrease of apoptosis of kidney tubular cells of a

mouse afflicted with an ischemia reperfusion injury. Furthermore, the mouse antisense compound (SEQ ID NO. 73) does not provide information regarding the structure of other compounds that will allow one skilled in the art to practice the claimed invention, namely inhibition of Fas and treatment or prevention of an ischemia reperfusion injury of a cardiac, renal, hepatic or skin allograft recipient.

The prior art teaches several known nucleic acid sequences of Fas originating from human, mouse or rat (see Ishiyama et al. J. Immunol 1998 161:4695-4701 and Munsch et al. JBC 275(6) 3867-3872 2000). The general knowledge in the prior art concerning Fas nucleic acid sequences does not provide any indication of what structure to what Fas will provide treatment or prevention of an ischemia reperfusion injury of a cardiac, renal, hepatic or skin allograft. Although the specification teaches one mouse antisense compound (SEQ ID NO. 73), the specification as filed nor the prior art provide a description as to what antisense compound for which version of Fas will provide treatment or prevention of an ischemia reperfusion injury in a cardiac, renal, hepatic or skin allograft recipient.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date sought, applicant was in possession of the claimed invention because the specification, while providing information on one mouse antisense compound (SEQ ID NO. 73), does not provide any other information or guidance as to what antisense sequence for which version of Fas will provide treatment or prevention of an ischemia reperfusion injury in a cardiac, renal, hepatic or skin allograft recipient.

Claims 78-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of a mouse ischemia reperfusion injury

of the kidney by administration of a mouse antisense compound (SEQ ID NO. 73), does not reasonably provide enablement for prevention of any ischemia reperfusion injury in any cardiac, renal, hepatic or skin allograft by administration of an antisense compound targeted to any version of Fas from any organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of preventing ischemia reperfusion injury in a cardiac, renal, hepatic or skin allograft comprising administering an antisense compound (SEQ ID NO. 73) targeted to a sequence encoding a mouse Fas. It must be noted that the scope of the claims are requiring a very high therapeutic standard, namely "prevention" of an ischemia reperfusion injury, as compared to merely treating or diminishing the effects of a reperfusion injury caused by ischemia.

The specification as filed teaches a mouse antisense compound (SEQ ID NO. 73) that inhibits expression of the mouse Fas. The specification also teaches an inhibition of Fas mRNA levels in murine hepatocyte cell lines transfected with oligonucleotide (see example 5 of the specification). Furthermore, the specification teaches that administration of a mouse antisense compound (SEQ ID NO. 73) targeted to mouse Fas decreased the expression of Fas protein levels in the livers of mice and a reduction in Fas was observed in the liver cells of mice who were given an antisense compound (SEQ ID NO. 73) before receiving a Con A induced liver injury (see examples 7 and 8 of the specification). Additionally, example 20 of the specification as filed teaches a mouse antisense model with an ischemia reperfusion injury of the kidney

and a correlation between administration of a mouse antisense compound (SEQ ID NO. 73) and a decrease in apoptosis of the tubular cells of the kidney as well as decreased levels of Fas mRNA expression in the tubular cells of the kidney. While the specification teaches a decreased level of mouse Fas mRNA observed in murine hepatocyte cells, murine liver cells and in the kidneys of mice that were administered mouse antisense compound (SEQ ID NO. 73) before affliction of an ischemia reperfusion injury, the specification as filed does not broadly teach the prevention or treatment of an ischemia reperfusion injury in a cardiac, renal, hepatic or skin allograft by administration of a mouse antisense compound (SEQ ID NO. 73) targeted to a nucleic acid sequence encoding mouse Fas.

The prior art teaches that Fas receptor-induced signaling is a mechanism that regulates apoptosis or programmed cell death and that alterations in Fas expression may lead to the loss of apoptotic functions in cells and tissues (see Nagata et al. Science 1995 Mar 10, 267:1449-1456). The prior art also teaches that Fas receptor-induced signaling regulates kidney cell apoptosis (see Ortiz et al. Nephrol Dial Transplant 1999 14: 1831-1834). However, neither the specification as filed nor the prior art recite what antisense to what Fas will broadly allow one skilled in the art to practice the invention, namely prevention or treatment of an ischemia reperfusion injury of a cardiac, renal, hepatic or skin allograft recipient by administration of an antisense compound targeted to any version of Fas from any organism.

The state of the art with regard to administration of antisense is very low

because there is a high level of unpredictability known in the art for therapeutic *in vivo* applications. Branch stresses that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" (TIB 23: 45-50 1998). Green et al. states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2). Jen et al. states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen et al. concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

Despite the improvements in the antisense technology over the past decade such as synthesis of more resilient, nuclease resistant oligonucleotides backbones, the

antisense technology still "faces several methodological limitations, including oligonucleotide stability versus binding affinity, delivery of oligonucleotides to the target cells, and non-antisense effects of oligonucleotides" (see Tamm et al. Lancet 2001; 358:489-97 pg 493 column 2). Opalinska et al. state "it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability (Nature Reviews Drug Discovery, 2002, vol 1, p. 503-514). The unpredictability of *in vivo* studies in the antisense art stems in part from the discovery that antisense oligonucleotides "distribute nonuniformly between different organs and even between different cell populations within a single organ. It is not clear what causes the differences or whether they reflect differences in the rates of uptake or differences in the ability to retain the [antisense oligonucleotides] by different cell types" (see Wang et al, Antisense and Nucleic Acid Drug Development 13:169-189 2003 pg 185 column 1).

As outlined above, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely prevention of an ischemia reperfusion injury by administration of an antisense compound targeted to any version of Fas from any organism. While one skilled in the art may be able to find an antisense oligonucleotide targeted to Fas and inject the antisense oligonucleotide into a mouse with an ischemia reperfusion injury, the specification as filed does not teach how to administer any antisense oligonucleotide to

prevent or treat reperfusion injury caused by ischemia as claimed. The specification as filed, specifically example 20, teach that systemic administration of a mouse antisense compound (SEQ ID NO. 73) showed that Fas expression and apoptotic activity in tubular cells were "significantly inhibited." Nowhere in the specification does it teach that because of the administration of this mouse antisense compound that ischemic reperfusion injury was prevented or treated and more specifically prevented or treated in a cardiac, renal, hepatic or skin allograft.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Therefore, in considering the total of the claims in view of the specification and the unpredictability in the art, they do not teach how the claimed antisense compound enters the cell, inhibits the expression of Fas, prevents the tubular cells of the kidney from undergoing apoptosis and ultimately prevention of an ischemia reperfusion injury. Thus, one of skill in the art would not accept on its face the successful delivery of any

claimed inhibitory molecule to Fas *in vivo* and further, prevention or treatment of an ischemia reperfusion injury, in view of the lack of guidance in the specification and the unpredictability in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Kimberly Chong
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